
The Comorbidity of ADHD and Autism Spectrum Disorders (ASDs) in Community Preschoolers

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Additional information is available at the end of the chapter

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Abstract

Symptoms of inattention and hyperactivity, features of attention-deficit/hyperactivity disorder (ADHD), have been frequently documented in children with autism spectrum disorders (ASDs) and often co-occur. Evidence indicates that 20-50% of children with ADHD meet criteria for ASD, and 30-80% of ASD children meet criteria for ADHD.

According to the DSM-IV, the essential features of Autistic Disorder (AD) are “the presence of markedly abnormal or impaired development in social interaction and communication and a markedly restricted repertoire of activity and interests”. Differential diagnosis of “Pervasive Developmental Disorder” (PDD: Autistic Disorder, Rett’s Disorder, Childhood Disintegrative Disorder, Asperger’s Disorder) and “Pervasive Developmental Disorder-Not Otherwise Specified” (PDD-NOS) is often difficult in the preschool child. This is particularly true when assessing verbal and nonverbal communication since both expressive and cognitive language are not yet established and there are many differences in their acquisition period among these children (before the age of three). As a result, many of these children are diagnosed with PDD-NOS not meeting the criteria for a specific type of PDD; this category includes “atypical autism” presentations that do not meet the criteria for AD. As a result, the concept of PDD-NOS has become a mixed bag. Often, diagnosis cannot be established before age three, delaying therapeutic interventions. Moreover, differential diagnosis between ADHD and PDD-NOS can be especially difficult, mainly in infant and young children. However, and following the recommendations of the DSM- IV, the ASDs diagnosis has been included among the exclusion criteria for the ADHD. Such exclusion has generated considerable controversy regarding the necessity and benefits of maintaining these separations.

At present, a new edition of the DSM has been published: DSM-5® (Fifth Edition, 2013). Among the advantages that this new manual provides are: i) further categorization of the persons affected and ii) the possibility of diagnosis before the age of three. The DSM-5 takes into account that limitations in language are not specific to autism. The new diagnostic category “Social Communication Disorder” appears separate from ASD, which does not seek to create a new subcategory.

In light of the new DSM-V criteria which allow a dual diagnosis of ASD and ADHD behaviors, in this chapter we will review the clinical overlap of these two conditions, particularly regarding their comorbidities in community pre-schoolers (generally categorized as PDD-NOS). We will also look into possible future research directions necessary to enhance our understanding of the etiology/genetics factors as well as the appropriate sequence of therapeutic interventions and pharmacological treatment (psychostimulant and nonstimulant medications) for the co-occurrence of these disorders.

Keywords: Autism, Attention-deficit/ hyperactivity disorder, co-occurance, comorbidities, pre-schoolers, dual diagnosis, therapy, research

1. Introduction

Symptoms of inattention and hyperactivity are features of attention-deficit/hyperactivity disorder (ADHD) that have been frequently documented in children with autism spectrum disorders (ASDs). Evidence indicates that 20–50% of children with ADHD fulfilled the criteria for ASD, particularly at preschool age, and 30–80% of ASD patients fulfilled the criteria for ADHD [1]. A shared genetic susceptibility has been suggested for both neurodevelopmental disorders [2].

According to the DSM-IV-TR [3], the essential features of autistic disorder (AD) are “the presence of markedly abnormal or impaired development in social interaction and communication and a markedly restricted repertoire of activity and interests”. Differential diagnosis of pervasive developmental disorder (PDD: autistic disorder, Asperger disorder, childhood disintegrative disorder, Rett disorder) and pervasive developmental disorder-not otherwise specified (PDD-NOS) can often be difficult in preschool children. This is particularly true when assessing verbal and nonverbal communication, since both expressive and cognitive language are not yet established and there are many differences in their acquisition period among these children (before the age of three). As a result, many of these children are diagnosed with PDD-NOS not meeting the criteria for a specific type of PDD. This category includes atypical autism presentations not fulfilling the criteria for AD. As a result, the concept of PDD-NOS has become a mixed bag; overuse of PDD-NOS has led to confusion in the diagnosis and contributed to the autism “epidemic”. Often, diagnosis cannot be established before age three, delaying therapeutic interventions. Moreover, differential diagnosis between ADHD and PDD-NOS can be especially difficult, mainly in infants and young children. However, following the recommendations of the DSM-IV, the ASD diagnosis has been included among the exclusion criteria for ADHD. Such exclusion has generated considerable controversy regarding the necessity and benefits of maintaining these separations. (For the conceptual history of modern-day ADHD and ASD, see Table 1).

At present, a new edition of the DSM (Diagnostic and Statistical Manual of Mental Disorders from the American Psychiatric Association) has been published: the DSM-5® (APA, Fifth Edition, 2013) [4]. The DSM-5 is principally intended as a handbook for clinical staff, making

reviews accessible for daily practice. Disorders have been classified with associated criteria to improve the accurate diagnosis of these syndromes. It should be noted that among the major changes in childhood disorders contained in the new edition are the following [5, 6] (see Table 2).

DSM	ASD	ADHD
DSM-I (1952) & DSM-II (1968)	No terminology for Pervasive Developmental Disorder or Autism. Closest denomination: Schizophrenic Reaction (Childhood category)	No term for attention deficit Minimal brain dysfunction Hyperactive Child Syndrome Hyperkinetic reaction of children
DSM-III (1980)	Pervasive Developmental Disorders (PDD): Atypical Autism, Infantile Autism, Childhood Onset PDD	ADD: Attention Deficit Disorder
DSM-III-R (1987)	Pervasive Developmental Disorders (PDD): Autistic Disorder, PDD-NOS	ADHD: Attention Deficit Hyperactivity Disorder
DSM-IV (1994)	Pervasive Developmental Disorders (PDD): Asperger disorder, Rett syndrome, Childhood Disintegrative Disorder, Autistic Disorder, PDD-NOS	ADHD: Attention Deficit Hyperactivity Disorder Identifies three ADHD subtypes: Predominantly Hyperactive-Impulsive type, Predominantly Inattentive type, Combined type
DSM-IV-TR (2000)	Diagnoses are the same, text amendment for PDD-NOS	Same diagnoses
DSM 5 (May 2013)	ASD is a new single condition with different levels of symptom severity. New diagnostic category: Social Communication Disorder	Presentation specifiers that map directly to the prior subtypes. Different levels of symptom severity

Table 1. Nosology Evolution and DSM History

DSM-5 vs. DSM IV	ADHD	ASD
CHANGES	ADHD does not fade at a specific age. The definition ADHD has been updated in DSM-5 to characterize more precisely the experience of affected adults.	One of the main changes in DSM-5 concerns ASD. The present revision of diagnosis constitutes a new, more accurate, and scientifically and medically useful way to diagnose subjects with autistic disorders.
CORE DOMAINS	The criteria have not changed from DSM-IV. Symptoms remain classified into two categories: inattention and hyperactivity/ impulsivity (including behaviors such as excessive talking,	According to DSM-IV, subjects were diagnosed with four separate conditions: Childhood disintegrative disorder Asperger disorder Autistic disorder

DSM-5 vs. DSM IV	ADHD	ASD
	<p>impaired organization skills, failing to pay close attention to details, wriggling, or inability to sit still and remain seated) In DSM-5 subtypes have been substituted with presentation specifiers that relate directly to the prior subtypes.</p>	<p>Pervasive developmental disorder not otherwise specified Using DSM 5 the different groups disappear. ASD is a new DSM-5 term reflecting the scientific consensus that the previously four separate conditions are actually one disorder, with several degrees of symptom severity within two core areas: 1) Deficits in social interaction and social communication 2) Restricted repetitive behaviors, activities and interests (RRBs) (*)</p>
SYMPTOMS	<p>DSM-5 uses the same 18 symptoms employed in DSM-IV and persist the classification into two symptom domains (hyperactivity/impulsivity and inattention). Children have to present with at least six symptoms from either (or both) the hyperactivity or impulsivity group of criteria and inattention criteria, whereas adolescents and adults (over 17 years of age) must have five.</p>	<p>ASD patients often present communication impairments that include incorrect interpretation of nonverbal interactions, inappropriate responses in conversation, or inability to build age-appropriate friendships. Besides, people with ASD tend to be highly dependent on routines, hypersensitive to environmental change, or focus intensely on inappropriate items. ASD symptoms seem to fall on a continuum ranging from mild to much more severe.</p>
AGE OF ONSET	<p>According to DSM-5, a number of the subject's ADHD symptoms have to appear before 12 years of age, whereas when using DSM-IV the age of onset was 7 years old.</p>	<p>According to the new DSM-5 criteria, ASD diagnosis requires the early presence of symptoms during childhood, even if such symptoms cannot be detected until a more advanced age. The present modification in the criteria promotes earlier diagnosis of ASD but also permits including subjects whose symptoms are not completely identified until social tasks surpass their capabilities. It is a relevant improvement from the DSM-IV criteria, which was focused on diagnosing school-age children with autism-related disorders. However, it still falls short to identify ASD in younger children.</p>
EXCLUSION CRITERIA	<p>ADHD symptoms can not appear only during the course of schizophrenia or another psychotic disorder and should</p>	<p>DSM-5 does not include exclusion criteria for subjects with ASD, because symptoms of ASD and ADHD tend to co-occur.</p>

DSM-5 vs. DSM IV	ADHD	ASD
	not be better explained by another psychiatric condition.	(*) Since both domains are required for ASD diagnosis, "social communication disorder" is diagnosed when no RRBs appear.

Table 2. Highlights of Changes of ADHA/ASD from DSM-IV-TR to DSM-5

- The chapter that includes "Diagnoses usually first made in infancy, childhood, or adolescence" in DSM-IV has been deleted and substituted in Section II (Diagnostic criteria and codes) of DSM-5 by the referred "neurodevelopmental disorders".
- Both ADHD and ASD are now classified together as neurodevelopmental disorders, which also includes some former DSM-IV "disorders first diagnosed in infancy, childhood, or adolescence" appearing across DSM-5.
- DSM-5 replaces the term "mental retardation" with *intellectual disability*, and the term *intellectual developmental disorder* appears between brackets to refer to the classification system of the World Health Organization.
- The DSM-5 communication disorders include a new condition: social (pragmatic) communication disorder.
- ASD is a new term in DSM-5 reflecting the scientific consensus that Asperger disorder, AD/autism, PDD-NOS, and childhood disintegrative disorder (formerly considered separate disorders) are actually all the same entity.
- Criteria for diagnosis of ADHD in the new edition are similar to those in DSM-IV. However, several subtle, but very important changes have been made in the DSM-5. Among the most notable are that diagnostic criteria now allow a comorbid diagnosis of ADHD with ASD. DSM-IV required "clear evidence of clinically significant impairment in social, academic, or occupational functioning"; this has been changed in DSM-5 to: "There is clear evidence that the symptoms interfere with, or reduce, the quality of social, academic, or occupational functioning." In addition, ADHD is now included in the neurodevelopmental disorders chapter of the text, rather than being grouped with the disruptive behavior disorders as it was previously.

Among the advantages that this new manual provides are: 1) further categorization of the persons affected and 2) the possibility of diagnosis before the age of three. DSM-5 takes into account that limitations in language are not specific to autism. The new diagnostic category, "social communication disorder", appears separate from ASD, which does not seek to create a new subcategory.

Keeping in mind the new criteria from DSM-5 that allow a dual diagnosis of ASD and ADHD behaviors, in this chapter we will review the clinical overlap of these two conditions, particularly regarding their comorbidities in early preschoolers (before the age of three, generally categorized as PDD-NOS). We will also look into possible new research perspectives to gain further insights into the etiology/genetic factors, as well as the appropriate sequence of

therapeutic interventions and pharmacological treatment (psychostimulant and non-stimulant medications) for the co-occurrence of these disorders.

2. Differential diagnosis of neurodevelopmental disorders

Neurodevelopmental disorders (NDDs) are impairments in the growth, development, and function of the brain that affect emotion, learning ability, and memory, and that unfold as the individual grows. This disorder is highlighted by characteristic deficiencies: cognitive impairment, delays in maturationally-influenced psychological features, overlap among NDDs, and genetic predisposition,

In DSM-IV, the chapter that includes “Diagnoses usually first made in infancy, childhood, or adolescence” has been deleted and substituted in DSM-5 by the referred “Neurodevelopmental Disorders” [4, pp. 229-272], which includes six categories:

- Specific Learning Disorder
- Communication Disorders
- Intellectual Disability (Intellectual Developmental Disorder)
- Autism Spectrum Disorder
- Motor Disorders
- Attention-Deficit/Hyperactivity Disorder

The recognition of the prevalence of comorbidities in NDD, particularly during the preschool years, is important in order to obtain a more complete and comprehensive vision of the range of abilities and deficits of a child without being limited by the possibilities of exclusion obsolete diagnostic criteria of DSM-IV. Especially since these conditions often overlap, an accurate differential diagnosis is needed to provide appropriate services. Where once our diagnostic manual (DSM-IV-TR) prevented comorbid diagnoses of disorders such as autism and ADHD, this exclusion is no longer present in DSM-5. This is the recognition that although symptoms can overlap, a child with autism and ADHD is clearly different from a child with autism alone and therefore, may require different intervention services [1, 5, 6].

In these early ages, neurodevelopment must be taken into account in all situations that may involve both learning difficulties and communication. In this way, NDDs in early childhood, as we highlight in their differential diagnosis, mainly include: intellectual disability, communication disorders, ASD, and ADHD.

2.1. Intellectual disabilities

The DSM-5 subclass includes:

- Intellectual Disability (Intellectual Developmental Disorder)

- Unspecified Intellectual Disability (Intellectual Developmental Disorder)
- Global Developmental Delay

“The choice of which category to use is determined in large part by the strength or clarity of the evidence that criteria are met” [4, pp 229].

- **Intellectual Disability (ID, Intellectual Developmental Disorder) 319**

DSM-5 introduces changes in name and criteria for intellectual disability, including a shift away from primary reliance on IQ scores:

Name. “Mental retardation” is replaced by *intellectual disability*. ID includes both intellectual and adaptive functioning deficits. The onset of this disorder takes place during development. Three domains are employed to assess severity: practical, conceptual, and social life skills.

Elimination of IQ-based Subtypes. In DSM-IV, intellectual function is standardly evaluated using culturally appropriate, comprehensive, psychometrically valid, and sound tests of intelligence that are individually administered (Mild = IQ 55–70; Moderate = IQ 40–55; Severe = IQ 25–40; Profound = IQ < 25). DSM-5 does not list mild, moderate, severe, and profound subtypes; but mild, moderate, and severe severity levels. Severity codes indicate the vision of the diagnosing clinician regarding the severity of adaptive functioning. IQ test scores are conceptual functioning approximations that may not be instrumental to evaluate the performance of practical tasks reasoning in real-life situations. However, according to the new DSM-5, a subject with severe social impairment (enough to be placed under the moderate category, for example) can be placed in the mild category due to the fact that they present an IQ reaching 80–85. DSM-5 puts less stress on the level of impairment (i.e., IQ scores) and more on the size and type of the intervention that has to be applied.

- **Mild intellectual disability:** This group includes roughly 85% of the individuals with ID, and it is more or less equivalent to the educational category previously referred to as “educable”, namely individuals within this group have the capacity to achieve some academic success.
- Children with this ID usually develop communication and social skills during the preschool period (0–5 years of age) and frequently cannot be distinguished from children without ID deficits until they are older. Therefore, initially learning problems can be attributed to deficits in attention, especially if also present with hyperactivity.
- When they reach their late teens, they usually meet elementary academic levels (up to grade six, approximately) or beyond if they count with enough support. Often, they manage to live independent lives in the context of their communities receiving minimal additional support, such as assistance with life decisions. For other skills such as nutrition, transportation, shopping, and finances, additional reminders, instructions, and time may be necessary
- **Moderate, Severe and Profound intellectual disability:** Usually, there will be no confusion in the differential diagnosis with ADHD, but comorbidity with ASD may exist.

Therefore, diagnosis of ASD now requires reference to intellectual ability: “ASD with or without accompanying intellectual impairment”.

- **Global Developmental Delay 315.8 (F 88)**

“This diagnosis is reserved for individuals < 5 years old, when clinical severity cannot be reliably assessed during early childhood” [4, p 230]. Criteria:

- failure to meet developmental milestones
- unable to be assessed using standardized tests
- re-assessment is required

- **Unspecified Intellectual Disability (Intellectual Developmental Disorder) 319 (F79)**

“This diagnosis is reserved for individuals > 5 years old, when assessment of the degree of ID by means of locally available procedures is rendered difficult or impossible because of associated sensory or physical impairments” [4, pp 231].

2.2. Communication disorders

Communication disorders in DSM-5 include novel and updated syndromes:

- Language disorder, which is a combination of DSM-IV mixed receptive-expressive, and expressive language disorders.
- Speech sound disorder replaces what was known as phonological disorder.
- Childhood-onset fluency disorder replaces the term stuttering.
- Social (pragmatic) communication disorder (SCD) is a newly coined pathology consisting of constant difficulties in the social uses of nonverbal and verbal communication (ASD must be ruled out).

We only make reference in this chapter to the new category, SCD.

- **Social (pragmatic) Communication Disorder (SCD) 315.39 (F80.89).**

SCD is a pragmatic disability, whose diagnosis is based on deterioration in the social usage of verbal and nonverbal communication in the child’s natural environment, which influences the development of discourse comprehension and social relationships and cannot be explained by poor skills in the areas of grammar, word structure, or overall cognitive capacity. Symptoms include problems with inappropriate responses in conversation, as well as difficulty in the acquisition and use of spoken and written language. Since the symptoms described in SCD were not defined in previous editions of DSM, many individuals with these symptoms may have been classified under the not otherwise specified category of pervasive development disorder [for review see 7].

Social communication can be defined as “the synergistic emergence of social interaction, social cognition, pragmatics (verbal and nonverbal), and receptive and expressive language processing” [8]. Pragmatics [in 9] is defined as “the range of communicative functions (reason for

talking), the frequency of communication, discourse skills (turn taking, topic maintenance and change), and flexibility to modify speech for different listeners and social situations". Rapin and Allen [10] coined the term "semantic-pragmatic deficit syndrome" to describe children who are notably loquacious, exhibit problems finding words, and have difficulty conversing, including maintaining the thread of discourse. Correspondingly, Bishop and Rosenbloom [11] began using the term semantic-pragmatic disorder to characterize children with difficulties to understand and follow conversation rules and could use unusual language or choice of words in their speech. However, it has been proposed that semantic deficits may not always co-occur with pragmatic deficits. Thus, the term "pragmatic language impairment" was coined to define subjects with deficits in pragmatics (though not necessarily semantics) [12].

Social communication disorders may correspond to a different diagnosis or may take place associated to other conditions. Pragmatic language impairment has been described in a variety of neurological diseases such as epilepsy [13], children with behavioral problems [14,15], and also in psychiatric and NDDs, including, among others, language learning disabilities, intellectual disabilities, ASD [16], and ADHD [17]. Children with pragmatic language impairment may be placed within a continuum between individuals with specific language impairment and those with the social communication deficits of ASD [16]. With respect to ADHD, it has been suggested that the primary symptoms of the disorder (e.g., hyperactivity, impulsiveness, inattention) may also impair their social communication skills, which, in turn, may cause further limitations in academic achievement, communication, and social participation [18, 19]. The standardized measures available for Test of Pragmatic Language are usually performed in children over 3 years old. A preschool version (birth to 4 years old) [20] provides exclusively descriptive information that can be employed to recognize weaknesses and strengths and to establish treatment aims.

In SCD, the reduced social communication capabilities are the cause of functional limitations in academic achievement, effective communication, occupational performance, or social participation, alone or in any combination of the aforementioned characteristics.

Symptoms have to appear in the early ages even if they are not identified until they are older when communication, language, or speech demands are beyond their capabilities. It should not be assigned to the ASD section because it corresponds to a type of patient showing related, but distinguishable symptoms (see [3]).

Advantages:

- Including SCD in DSM-5 may drive further research into social (pragmatic) communication disorders using the operationalized diagnostic criteria, and thus aid in reaching a better understanding and documentation of the fundamental features and validity of SCD.
- Will help individuals with these symptoms access suitable treatment adapted to their impairment.
- Field trials from DSM-5 provided evidence of SCD, indicating that the lower ASD diagnoses in DSM-IV could be explained by a shift to the SCD diagnostic category [21].

- It is likely that individuals with social communication and/or pragmatic language disability were diagnosed as DSM-IV PDD-NOS.

Drawbacks:

- The scarcity of longitudinal research reduces our chances to extrapolate from previous literature to SCD.
- The standardized measures available for Test of Pragmatic Language are usually performed in children over 3 years, and a preschool version for children from birth to 4 years old.
- The steps to follow would be to confirm the efficacy of the criteria for SCD, as well as assessing the impact of cultural and socio-demographic factors on its appearance.

2.3. Autism spectrum disorder (ASD) 299.00 (f84.0)

Autism, a debilitating neurological handicap in children, is a highly heterogeneous set of disorders with wide variations in symptom severity, intellectual level, and functional disability. It is a multifactorial disorder implicating a wide range of environmental risk factors and genetic predispositions. No definitive biological markers are available for autism, therefore, in most cases, diagnosis is based on a variety of behavioral signs. Since autistic patients may present with very diverse symptoms and features, autism is thought of as a spectrum disorder [22].

The ASD diagnosis is of great concern to the practicing pediatrician because its frequency has been increasing for decades, with a surprising 556% rise in pediatric prevalence reported between 1991 and 1997 (higher than that of Down syndrome, cancer, or spina bifida). Researchers cannot agree on whether the trend is a result of increased awareness, improved detection, and changing diagnostic criteria with expanding definition, or of new environmental influences [23, 24].

In multiple communities in the United States [CDC surveillance data 2010, see 25], the overall prevalence of ASD was 14.7 per 1,000 (one in 68) 8-year-old children. Overall, prevalence estimations for ASD ranged across locations from 5.7 to 21.9 per 1,000 8-year-old children. Consistent with previous reports, there was significant variety in ASD prevalence according to gender, geographic region, racial/ethnic group, and intellectual ability. It is unclear in this study to what degree the variation in prevalence might be due to diagnostic methods, lack of recognition of ASD symptoms in certain ethnic/racial groups, socioeconomic disparities in access to therapeutic and community services, and regional differences in clinical or school-based practices.

The relevance of accurate diagnosis of autism has become greater than ever, particularly in view of the increasing prevalence [26], elevated costs for both family and society [27], and accepted importance of early identification and intervention in individuals with autism. The classification systems used strongly affect prevalence studies, and it is important to consider the changes that have occurred at this level when analyzing the possible causes of the increase in pervasive developmental disorders [28].

- **Classically in DSM-IV**, Pervasive developmental disorders (PDD) encompass a heterogeneous group of children typified by severe and pervasive impairment in a number of developmental areas: 1) communication skills, 2) reciprocal social interaction skills, and 3) the presence of stereotyped activities, behavior, and interests. The qualitative incapacities described for these conditions vary considerably according to mental age or developmental level of each child. The specific pathologies included five subtypes in this section: autistic disorder (AD), Asperger disorder, childhood disintegrative disorder (CDD), Rett disorder (RD), and pervasive developmental disorder-not otherwise specified (PDD-NOS). These conditions normally become apparent in the early postnatal years and are frequently associated with certain level of mental retardation (now called *intellectual disability*).

DSM-IV is not the “Gold Standard”. Among the concerns that have arisen on the application of DSM-IV that stand out [29–31] are:

- Validity of the PDD category. Symptoms are not pervasive. They are specific (selective or greater) impairment in social interaction plus restricted, repetitive behaviors/fixated interests.
- Validity of certain diagnoses (e.g., childhood disintegrative disorder category)
- Consistency in diagnosing (e.g., high-functioning autistic disorder vs. Asperger).
- Current diagnostic guidelines may not fulfill all needs from community evaluators [32].
- The usage of some diagnoses may not be completely appropriate (e.g., PDD-NOS as mild NDD, Asperger as “odd” behaviors)

Recommendations from the Autism and Developmental Disabilities Monitoring (ADDM) Network include improving strategies that meet the needs for 1) amply accepted standardized, methods for documenting both ASD diagnosis functional limitations and the severity of ASD; 2) improved documentation and recognition of ASD symptoms, concretely among both boys and girls, children from all racial/ethnic backgrounds, and children with no intellectual disability; 3) reducing the age of first evaluation for and diagnosis of ASD, including the age at which children are enrolled in community-based support systems [25].

- **The new DSM-5: Changes in the diagnosis of autism** (see [4])

These changes arise to unify and standardize the criteria to better define ASD, to increase validity and appropriateness of the use of diagnoses, and to obtain an earlier diagnosis [33–35].

1. **There is a single category of ASD** instead of five subtypes (Figure 1). The term PDD has been deleted. Scientific evidence and clinical practice indicate that the single spectrum is a better reflection of the symptom picture, time course, and response to therapy. While it is reliable and valid to distinguish ASD from typical development, differentiating between conditions within the spectrum is not. Thus, Asperger and PDD-NOS are used interchangeably, as it also happens with high-functioning autism (HFA) and Asperger [29].

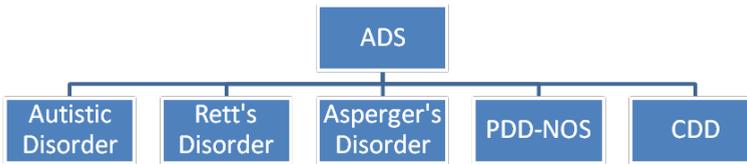


Figure 1. From PDD to ASD.

- Deletion of Asperger disorder: Still, to date, there is little clinical or research evidence that Asperger disorder is qualitatively distinct from other autism diagnoses at the symptom level, or that the new criteria will under-identify high-functioning ASD [36]. This situation has led to difficulties in deciding whether to use the terms “HFA” or “Asperger” for diagnosis. Diagnostic biases are apparent, with rich, white males receiving Asperger dx, while poorer, non-Caucasian populations receive PDD-NOS diagnosis (See site differences in CDC surveillance data [25]).
- Elimination of childhood disintegrative disorder (CDD): New data show that developmental regression in ASD is a continuous variable, encompassing a wide range in the timing and types of skills lost, as well as in the developmental milestones that were accomplished before regression. Since CDD is a rare diagnosis, systematic evaluation is difficult; however, review of accumulated literature indicates that CDD differs notably from other ASDs, including in the abruptness and severity of the deterioration, as well as co-occurrence with physical symptoms such as loss of bladder and bowel control. Thus, CDD diagnosis requires searching for the neurological impairments associated with it.
- PDD-NOS: This subset should be employed when there is severe and widespread impairment of reciprocal social interaction in the presence of disability in either verbal or nonverbal communication skills, or associated with stereotyped behavior, activities, and interests without meeting the criteria for a specific PDD. The distinctions among the disorders have been inconsistent and often based on variables other than the criteria for the diagnosis. For example, this category includes “atypical autism” (presentations that do not meet the criteria for autistic disorder because of late age of onset, atypical symptomatology, or subthreshold symptomatology). These changes were necessary taking into account: 1) Overuse of PDD-NOS leads to diagnostic confusion (and may have contributed to the autism “epidemic”); 2) Overlap of PDD-NOS and Asperger disorder.
- At present, ASD is defined by “specific sets of behaviors, not etiologies”, therefore, inclusion of Rett disorder is atypical. Patients with Rett disorder can be diagnosed as having ASD but the specifier “ASD associated with a known medical or genetic condition or environmental factor” should be used to indicate that ASD are related to Rett.

2. The three domains are combined into two.

Nowadays, ASD is considered an NDD diagnosed according to a shared group of behaviors and is best defined as a new single condition/diagnostic category showing diversity in the severity of its symptoms that can be assigned to two core domains (Figure 2):

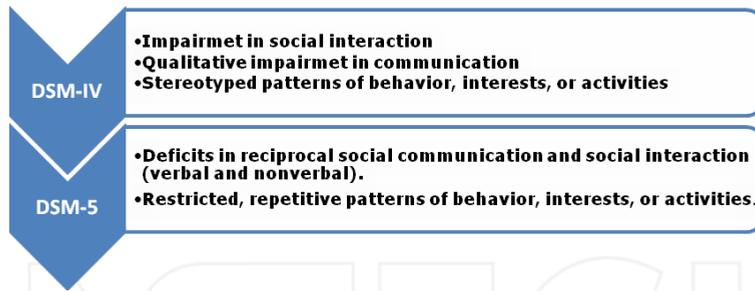


Figure 2. ASD: The three domains are combined into two.

- a. Social interaction and social communication deficits. The rationale is that deficits in communication and social behaviors are inseparable. The social communication domain results from combining the principal symptoms from the DSM-IV social and communication domains. By doing this, language skills not employed in the context of social communication reduce the relevance.
- b. The second major criterion remains restricted repetitive behaviors, interests, and activities (RRBs).

ASD by definition encompasses pragmatic communication problems, but also includes RRBs. Because both components are required for diagnosis of ASD, taking all this into consideration, SCD is diagnosed if no RRBs are present.

3. **Diagnostic Criteria:** 12 symptom-items in the DSM-IV are reduced to 7. Symptoms are not deleted, but those criteria that describe similar characteristics are merge. There must be five out of seven criteria to make the diagnosis of ASD.
4. **Sensory processing:** RRBs are expanded to include “abnormalities in sensory processing”.
5. **The broadened age of onset criteria:** Symptoms must be present in the early developmental period. To meet the requirements for criterion C in DSM-IV, symptoms must start prior to 3 years of age. DSM-5 only stipulates that symptoms start in early childhood, cautioning that they “may not be fully manifest until social demands exceed capacity”, that is to say during middle-school years, late adolescence, or young adulthood. The results of Guthrie et al. [37] may be helpful to illustrate the manifestations of autistic symptoms during development. They assessed a sample of 237 children with ASD, between 12 and 30 months of age using ADOS-T, and found that autism symptoms can be divided and best deconstructed into the two-factor DSM-5 model, which supports the DSM-5’s reorganization of symptoms. The fact that these results in young children coincide with earlier studies in older children and adults indicates that the structure of autistic symptomatology may be similar across the developmental stages.
6. **Specify current severity:** Level 3: Requiring very substantial support; Level 2: Requiring substantial support; and Level 1: Requiring support.

7. **The addition of “specifiers”** to describe features such as “with or without intellectual impairment”, “with or without language impairment”, “associated with known medical or genetic condition” (deletion of Rett syndrome as a specific ASD), and “with catatonia”.

Advantages:

- They are specific to the social-communication domain plus restricted, “repetitive behaviors/ fixated interests”. The criteria “Qualitative impairment in communication” disappears.
- ASD is a single spectrum disorder; however, it presents important individual variations. DSM-5 incorporates: cognitive abilities (IQ), clinical course and pattern of onset, severity of ASD symptoms, etiologic factors, and associated conditions. Clinicians will be likely to include these observations as “diagnostic specifiers”.
- DSM-5 criteria present higher specificity when compared to DSM-IV-TR criteria (0.97 vs. 0.86). This superior specificity may decrease false positive diagnoses, which is especially important in clinical settings where base rate tends to be low [38].

Drawbacks:

- Sensitivity is lower (0.81 vs. 0.95) in DSM-5. Therefore, sensitivity has been “sacrificed” to increase specificity. Loosening the DSM-5 criteria by reducing one symptom criterion improved sensitivity (0.93 vs. 0.81), causing a minor specificity decrease (0.95 vs. 0.97). It would be advisable that Phase II of DSM-5 testing would incorporate loosened criteria, which will prevent up to 12% of ASD-affected people, mainly females, from being potentially overlooked. Less stringent DSM-5 criteria may improve ASD diagnosis, reducing societal costs via adequate early identification and improving treatment resources [38]. Other studies demonstrate that a diagnostic algorithm following the DSM-5 criteria and adapted to age and ability level variations is able to achieve good levels of both specificity and sensitivity [39].
- Merging Asperger disorder and PDD-NOS into a single broad ASD ignores singularity and identity of the Asperger disorder. There is at least one study indicating that the DSM-5 draft criteria were less sensitive identifying patients that were already diagnosed with AS with an ASD [40]. Thus, this proposed change has generated considerable apprehension from both patients and their families, who are concerned that individuals diagnosed with Asperger disorder will be orphaned or receive inappropriate service provision [41]. Due to the fact, that AS patients possess at least average intelligence, they may find themselves a therapeutic “no man’s land” and not considered for disability services [42]. By contrast, other studies evaluate an important aspect of this controversy, namely symptom continuity between individuals with Asperger disorder and other ASD cases, by explicitly testing conflicting views of the nature of autism symptom structure. They have suggested that most children diagnosed with ASD using the DSM-IV would also be diagnosed as such employing the DSM-5 criteria [38, 43].
- Research studies from before and after DSM-5 will not be comparable. Important discontinuities in diagnostic practice create significant problems both for the clinical and research fields. It is not yet clear what the impact that these changes in the DSM-5 may have [31].

2.4. Attention-deficit/hyperactivity disorder (ADHD)

ADHD is considered the most frequent neurobehavioral childhood disorder. According to DSM-IV TR criteria, between 8% to 12% of school-age children could be diagnosed with ADHD [44]. However, there is a wide spread notion that ADHD is overdiagnosed. Although, the review of prevalence studies and research on the diagnostic process does not support the concept that ADHD is systematically overdiagnosed [45]. Some authors have proposed that ADHD should not be a disease as such, but rather a group of symptoms converging in a behavioral pathway for a series of psychological, emotional, and/or learning problems [46].

ADHD now falls under the Neurodevelopmental Disorders chapter, instead of being included within the disruptive behavior disorders, i.e., Oppositional Defiant Disorder and Conduct Disorder. This change accords better with the current concept of ADHD. ADHD is identified by a behavioral pattern, present in a variety of settings (e.g., school and home) that may affect performance issues in educational, work, or social settings. The threshold for meeting the diagnostic criteria for ADHD has been lowered slightly [47, 48].

Changes to ADHD in DSM-5:

1. **Core symptoms:** The general structure of the two dimensions of ADHD, inattention and hyperactivity/impulsivity, remains unchanged and DSM-5 retains the exact DSM-IV wording of all 18 symptoms. However, DSM-5 adds developmentally appropriate new exemplars to the criterion items to facilitate the application of these symptoms across the life span, more appropriate for children, adolescents, and adults.
2. **Age of onset criteria** of the disorder: The onset criterion has been changed from “symptoms that caused impairment were present before age 7 years” to “several inattentive or hyperactive-impulsive symptoms were present prior to age 12”. Furthermore, DSM-5 only requires that symptoms are present by age 12, not that they necessarily create impairment by this age, as in DSM-IV. The combination of older age of onset and removing the impairment requirement is clearly more lenient.
3. **Number of symptoms required and duration of symptoms:** A symptom threshold change has been made for adults by reducing the number of criteria that patients aged 17 years or older must fulfill for diagnosis, with a cutoff of five symptoms instead of the six required for younger persons, both for inattention and for hyperactivity/impulsivity. As in DSM-IV, it is required that symptoms last for 6 months or more, and keeping at a level that would not overlap with the standard development
4. **Multiple settings requirement:** The cross-situational requirement has been reinforced with “several” symptoms for every setting.
5. **Need for clinically significant impairment.** In DSM-IV, symptoms had to affect least two settings (“the behaviors must create significant difficulty in at least two areas of life, such as home, social settings, school, or work”). Therefore, symptoms were required to cause impairment in several contexts (e.g., both home and school), as well as affecting the functional ability of the child in more than one context. DSM-5 has revised this to “several inattentive or hyperactive-impulsive symptoms are present in two or more settings”.

Therefore, symptoms only have to appear in more than one setting and it is not required that they affect the subject's functioning in several contexts. This is less demanding too, and increases the chance to receive a full ADHD diagnosis, thus raising the percentage of the population who meets the diagnostic criteria.

6. **Presentations:** In DSM-5, subtypes have been substituted by presentation specifiers that correspond to the former subtypes in order to employ terms that accord with the change and fluidity that the disorder may display in a given patient across time. DSM-5 defines three presentations of ADHD according to the presence or absence of specific symptoms: hyperactive-Impulsive presentation, inattentive presentation, and combined presentation.
7. **New requirement to specify severity:** DSM-5 requires the severity of the disorder to be graded in the affected person, since ADHD symptoms impact each individual in varying degrees. Clinicians can specify the severity of ADHD presentation as mild, moderate, or severe, according to DSM-5 criteria:
 - Mild: A minimal number of symptoms are present that result in only minor impairment at school, work, home, and/or in social contexts.
 - Moderate: The impairment or symptoms are between mild and severe.
 - Severe: A large number of symptoms show a higher level than required to have diagnostic value, or various symptoms are markedly grave, or they severely undermine the person at school, work, home, and/or in social settings.

It must also be recognized that the degree of severity and how ADHD manifests itself can vary during the patient's lifespan, which implies the chance of a partial remission of ADHD.

8. **Comorbidity:** DSM-5 introduces an important and, generally, positive change related to comorbidity: the elimination of ASD as an exclusion criterion for the diagnosis of ADHD. In its revised ADHD diagnostic criteria, DSM-5 recognizes the frequency of this co-occurrence (particularly at a young, pre-school age), and allows, for the first time, a comorbid diagnosis of ADHD with ASD.
9. **New categories for persons not meeting full criteria.** The DSM-IV included a category called ADHD Not Otherwise Specified (NOS) for subjects showing notable symptoms but falling short of the required criteria. This has been revised to Other Specified ADHD and Unspecified ADHD in the DSM-5. The Other Specified category is employed when full the criteria are not reached, the clinician is able to determine the reason why full criteria were not met and the symptoms that do appear impair functioning in a clinically significant way.

Advantage:

- Comorbid diagnosis with ASD. This new disposition will pave the way for a more scientific approach to the overlap of these disorders, as well as enable a more appropriate clinical treatment of these children.

Drawbacks:

- The modifications introduced will probably raise the prevalence of ADHD, particularly in adolescents and adults, and perhaps also in children [49]. However, those changes are supported by clinical and epidemiological data and are unlikely to result in over-diagnosis [48].

3. Developmental period in preschool children

In the field of psychiatric disorders there has been a traditional delay in the systematic research dealing with infants and preschoolers (0 to 5-year-old children) in comparison with that studying school-age children, adolescents, and adults. To facilitate research on the preschool and infant ages, the development of clear and specific diagnostic criteria that can be confidently utilized within standardized measurements across a variety of samples is essential. In 2000–2002, an independent research committee elaborated the first Research Diagnostic Criteria-Preschool Age (RDC-PA), with the aim of promoting systematic study of psychiatric disorders in younger children [50].

The DSM model, with some revision to address the child's developmental level, appears to provide a valid means of differentiating typical behavior problems in preschool children from atypical disruptive conduct that is impairing. Systematic research is required to standardize the revision of current assessment tools so that they can be adapted for use with preschool children and to develop methods that are more clinically sensitive for determining a child's development level and for employing observational data in assessment [51].

Therefore, in young children, it is very important to recognize changes that may occur in the early stages of learning, especially in language acquisition and behavioral symptoms, which could already be identified as prodromal symptoms, followed by a correct differential diagnosis of these entities.

3.1. Development of language according to the stages of acquisition

The development of both language and communication is an intricate process affected by multiple genetic and environmental factors. Diagnostic criteria for NDDs (e.g., communication disorders, language Impairment, dyslexia, ASD, and ADHA) often include impairments in communication and language skills. These complex disorders are polygenic with a relevant genetic contribution to both types of skills. Language acquisition is the process by which human beings acquire the capacity to perceive, comprehend, produce, and use words and sentences to communicate. Humans' the early years, beginning at birth, are critical to future development of the skills required. Language acquisition needs to be stimulated in every way to generate a solid base to build upon as the child develops. There have been numerous investigations in this area, and several models for learning language have been developed based on neural networks, computational models, and other connectionist approaches [for review see 52–55]

Subject literature provides guidelines for when age-specific language features are acquired on average, but different authors cite different milestone dates, depending on where they conducted their research. Therefore, it is important to note that dates, in terms of specific linguistic milestones, are not concrete and can vary slightly from child to child. In accordance with published data, we can identify six basic stages of language acquisition occurring between ages 0 to 5 years, which coincide with the preschool stage. These ages are divided into two cycles: first cycle, between 0 and 3 years (in toddlers); and a second cycle, ranging from 3 to 5 or 6 years old, prior to the start of mandatory education.

The first cycle

- **Prelingual stage (0-6 mo):** Occurs before the use, acquisition, or development of language. Infants practice the pragmatic component of language use (e.g., by making eye contact with adult caretakers and exchanging sounds in something resembling a conversation). The "normal" child concentrates on the center of the face, or the region of the eyes. In NDD, there is a continuous and general deficiency in reciprocal social interaction. A notable disability in a myriad of nonverbal forms of social interaction and communication may occur (e.g., facial expressions, eye-to-eye contact, gestures, and body postures).
- **Babbling and canonical babbling stage(6–12 mo):** Babbling (also known as twaddling) is a stage of language acquisition during development when the child seems to be exploring their capability to produce articulate sounds, but still not being able to utter recognizable words. Syllable patterns start to emerge. Infants begin to distinguish between the different sounds, from vowels (V) to consonant and vowel (CV) syllables. This phase is considered to be the beginning of the canonical stage. During the canonical stage, babbling consists of repeated sounds containing alternations of consonants and vowels, progressing through such syllable types as VCV, VC, and redup of syllables (CVCV) and variegated syllables; children start to acquire the phonemes of the language.
- **One-word utterances/holophrastic stage (12–18 months):** By about one year of age, infants start saying their first words. These one-word utterances are defined in the literature as "holophrastic" since they have been interpreted as to serve the same purpose of longer word expressions in adults.
- **Two-word utterances (approx. 18–24 months):** The two-word stage is defined as a child using (quite obviously, as stated in the title) two words to form a sentence.
- **Telegraphic stage (2–3 years):** When children have acquired and start to use multiple-word utterances. At this stage, some of the children's utterances are grammatically correct.

The second cycle

- By about 5–6 years of age, children have acquired almost normal speech, with good command of syntax and semantics. In later stages, development of vocabulary and pragmatics takes place. Pragmatic development highlights children's motivation to acquire language in the first place, as it serves different purposes and functions. Pragmatics are not acquired immediately, nor does it take a short period of time for a child to acquire them. This process is on-going until the age of approximately 10 years. In AD patients that have

acquired speech, it can be found either repetitive, stereotyped/idiosyncratic language, or pronounced disability sustaining or initiating a conversation with other individuals.

As already mentioned, developmental milestones and particularly social communication abilities, language acquisition, and proper speech occur at different age ranges amongst children, therefore diagnosis of pathology at early ages can be hindered. In AD, there may be either total absence or a delay in the development of speech.

The classical criteria for AD require abnormal functioning in communication skills, which has been one of the reasons that AD was not usually diagnosed until the second cycle of preschool age. Therefore, although many children did not meet all the criteria, they were included in AD generally categorized as PDD-NOS; overuse of PDD-NOS has led to misdiagnosis and may have helped in the autism “outbreak”. In the new classification of ASD, communication (verbal and nonverbal skills) is excluded; by removing this requirement, possibility of diagnosis before the age of 3 is increased.

In recent years, work on identifying prodromal symptoms of ASD has offered a powerful avenue for studying the emergence of “*ASD in statu nascendi*”. At 6 months, ASD prodromal symptoms include a reduced capability to spontaneously pay attention to people and their activities [56–59]. At 12 months, a large proportion of infants posteriorly diagnosed with ASD show clinically relevant delays as well as dysfunction in various fields, including: vocalizations, social smiling, and eye contact [60–63], initiation of requesting and joint attention [62], object exploration [64], response to name [65], and responses to others’ distress [66–68]. However, many of these symptoms described for ASD can also occur in children with ADHD or intellectual deficit, so caution is needed before a definitive diagnosis [69].

Sociocultural and individual factors influence body language, facial expressions and eye contact, and social communication behaviors in preschoolers and there is an ample spectrum of norms that are considered acceptable within and across cultures, families, and individuals [70]. Young children with SCD can sometimes present with symptoms similar to ADHD or ASD, so it is necessary to establish screening tests for comorbid conditions. Children diagnosed with pragmatic language impairment may be placed within a continuum between individuals with social communication deficits associated with ASD and those presenting with the specific language impairment [16].

The criteria for PDD-NOS diagnosis according to DSM-IV required the presence of impaired reciprocal social interaction and either deficient communication skills or stereotyped behavior, activities, and interests. Subclinical symptoms were also allowed in the PDD-NOS category. It is therefore possible that, when applying the DSM-IV criteria, children with social communication and/or pragmatic language impairment were diagnosed as PDD-NOS.

The DSM-5 Communication Disorders include a new condition, SCD; so far fewer studies have been conducted to determine the extent of the problem. Additional research is necessary to discern the consequences that pragmatic language impairments and SCD have on neuropsychiatric disorders, problematic behaviors, and the acquisition of academic skills. To reliably diagnose SCD, children must have already acquired suitable language and speech capabilities (i.e., present by 4–5 years of age in standard language development) in order to identify

particular verbal pragmatic deficiencies. Therefore, samples from preschool- and school-age children should be employed in future research to establish a baseline for symptom manifestations. Developing and/or validating assessment tools to track and measure SCD traits will be invaluable to follow the course of the disease [7].

3.2. Control processes in behavioral domains

Although autism tends to appear during the first 1–2 years of life, ADHD is nearly impossible to diagnose along this period. Hyperactivity and inattentiveness are features shown by almost all toddlers, thus making ADHD very difficult to diagnose reliably until early childhood (although it is often possible during the preschool period) [71]. Children demonstrate dramatic gains in control processes between the ages of 3 and 6. During this developmental period, children begin to actively develop rudimentary regulation skills in affective, cognitive, and behavioral domains via rapidly developing limbic and neocortical circuitry [72] and in the context of parental socialization [73]. The determination of clinical significance of behavioral symptoms in the preschool period is complex due to the ample diversity usually found for these features.

Clinical experience and empirical data indicate that the criteria proposed for ADHD are largely applicable to children 3–5 years of age, whereas there is less evidence regarding their applicability to children under 3 years of age. Preschool children diagnosed with ADHD are similar with school-age ADHD youths in impaired functioning, high rates of comorbid psychopathology, and the quality of the disorder, despite the age difference [74]. Disorders of dysregulation can be first reliably diagnosed during this developmental period [50]. Hyperactivity-impulsivity may be a particularly prominent behavioral manifestation of preschool ADHD at home, whereas inattention may be more salient at the school setting [75]. Cognitive control has been found to be significantly associated with affective control (but not with effortful control) as a prominent form of control during early childhood in children with ADHD [76].

Furthermore, in a prospective population-based study, the Avon Longitudinal Study of Parents and Children (ALSPAC), in which subjects were recruited in the prenatal period (13,988 children alive at 12 months), results for boys indicated that autism overlapping with hyperactivity symptoms may contribute to problems with pragmatic language. This was not the case for girls or for socio-emotional difficulties [77]. In adults, by contrast, the co-occurrence of autistic and ADHD traits is not characterized by hyperactivity or impaired social skills, routine preferences or imagination. Instead, the connection between AD and ADHD is determined by common attention-related deficiencies (attentional switching capacity and lack of attention) [78].

Other studies have also found impaired facial affect recognition and empathy in children with ADHD [79, 80]. Some of the symptoms, such as lack of eye contact, can occur in different diseases and can be used to diagnose various behavioral and reading disorders: visual disturbances, intellectual disability, autism, ADHD, and dyslexia. In early childhood, when “impairment in social interaction or restricted repetitive and stereotyped patterns of behavior” is still not well established, sometimes it is particularly difficult to establish an appropriate differential diagnosis between these categories. There is little

research available on pre-school children with ADHD for the purpose of determining early ASD comorbidity, possibly because while ASD is often diagnosed at pre-school age, diagnosis of primary ADHD is frequently postponed to late pre-school or early school age [1]. No population-based study on ASD diagnoses in children with a primary clinical diagnosis of ADHD has been performed to date [81].

4. Overlap of ADHD and ASD

Although their core diagnostic criteria do not explicitly overlap, lately, an increasing number of studies provide evidence for an elevated degree of comorbidity between ADHD and ASD, with different levels of symptom severity. In DSM-5, the diagnoses of AD and ADHD will not be mutually exclusive any longer. This provides the basis for more differentiated studies on overlap and distinction between both disorders. [For review see 1, 81–85].

ADHD and ASD are more frequent in boys than in girls, and both emerge, at least to a certain degree, at preschool age. Research on the co-occurrence of ASD and ADHD has focused on older children despite the fact that characteristic ADHD and autistic behaviors appear already in early childhood. Clinicians have been able to recognize behavioral characteristics, such as social deficits, in children with ADHD hyperactivity among children with ASD for a long time. However, it is only in recent years that research investigating their comorbidity has burgeoned [82].

For example, the percentage of subjects with ASD meeting the criteria for ADHD was 30–31% for autism [86, 87] and 45% for PDD-NOS [88]. In a parallel way, high levels of autistic traits have been found in populations of children with ADHD [89] and with hyperkinetic disorder [90]; these autistic symptoms in ADHD are higher than in healthy control children [91]. Studies of clinical samples with ASD have also differentiated between ADHD subtypes and observed a prevalence of approximately 20% inattentive and 10% combined ADHD subtype in children with ASD [92]. The overlap was also significant for suspected cases (22% of children with suspected ADHD met criteria for ASD, 41% who met criteria for ASD had suspected ADHD) [93].

Contrary to the common belief that PDD-NOS is heterogeneous, the vast majority (97%) of patients presenting PDD-NOS had the same distinct pattern of symptoms, which consisted of deficiencies in social communication and reciprocity, unaccompanied by relevant repetitive and stereotyped behaviors (RSB). They had comparably severe, but more circumscribed, social communication deficiencies than AD or ASD patients, with lower number of non-social autistic symptoms, e.g., visual-spatial, feeding, and sensory impairments. These subjects seem to present a different type of autism that is more than just a less severe form of one symptomatology continuum. According to the current guidelines for DSM-5, requiring the existence of RSBs for every PDD diagnosis, PDD-NOS should be excluded from the autistic spectrum [94].

Currently, there is increasing interest in investigating the overlap of ADHD and ASD in terms of common neurobiological substrates, associated clinical comorbidities/neuropsychological

deficits, neural correlates, and shared genetic susceptibility. Therefore, we should ask some questions: Are both disorders distinct manifestations of the same underlying risk factor(s)? Is it possible that different subtypes within and across disorders do exist, for example, a subtype of ADHD combined with atypical autism or PDD-NOS, which may also show specific underlying risk factors? Do the disorders share neuronal circuitry?

4.1. Associated clinical comorbidities ADHD/ASD

The diagnosis of both ADHD and ASD is based on behavioral symptoms. Both conditions frequently encompass deficiencies in communication with peers, attention, various degrees of restlessness or hyperactivity, and impulsivity. The significance of the presence of clinical overlap regarding the underlying neurobiology and phenotype is not well known. Both syndromes are known to present genetic susceptibility, showing comorbidity across family members as well as within the same individual, and both conditions bring about significant academic, behavioral, adaptive, and emotional impairment at home, at school, and in other places [95].

ADHD behaviors and autistic-like features have been reported to present a positive significant correlation in a sample of community two-year-old children. The correlation between ADHD behaviors and autistic-like features was found lower in older children when compared with young adults ($r=0.23-0.26$ vs. $r=0.48-0.57$), indicating that the covariance of ADHD/ASD increases with age [96]. This can possibly be attributed to the fact that not all the characteristic behavioral types for ADHD and ASD have appeared yet in children, which makes less reliable the measurement of these behaviors when compared to adults.

Most reports using factor analysis to study ASD have found at least one factor connected with RRBs or "non-social" behavior and an independent factor connected with separate social-communicative features [97]. To the best of our knowledge, there are no publications employing factor analysis investigating autistic features in groups of children diagnosed with ADHD and, therefore, whether the existence of ADHD has any effect on the type of autistic traits remains to be elucidated.

Preliminary results suggest that, particularly in young children between 2 and 5 years, a worsening of ASD syndrome in children with ADHD is related to lower full-scale IQ, enhanced anxiety, oppositional and conduct symptoms, general motor problems, and working memory deficits [79, 98]. The risk for increased severity of psychosocial problems increases, as well as greater delays in adaptive functioning [99, 100]. These connections remained after correcting for ADHD severity, indicating that the severity of comorbid autistic traits is regulated independently from ADHD [101].

Existing data indicate that pragmatic language deficiencies seem to be similar both in children in the ASD spectrum and ADHD [102]. Both conditions also often show executive function (EF) attention deficits as well as response inhibition impairment. HFA and ADHD hardly differ in their EF measures. However, the HFA group showed more impairment in planning and cognitive flexibility when compared to the ADHD group [101]. Another study found that children with ASD and children with ADHD were indistinguishable as far as emotional

recognition and theory of mind, which further underlines the neuropsychological similarities between these two syndromes [103].

Although social difficulties are not considered central for ADHD diagnosis, the truth is that children with ADHD present significant social problems: they tend to be more frequently rejected by their peers (approximately 50–60%), and they do not have as many friends [104]. Research in the recent years indicates that many individuals with ADHD may present social deficiencies that are in line with those found in ASD. Cantwell [105] described a form of social impairment in ADHD as a “lack of savoir faire,” and calculated that this social ingenuousness may be present in about 20% of children and adolescents with ADHD. In children with ADHD as their primary diagnosis, the degree of autistic condition related to the severity of ADHD subtype, subjects with the combined type of ADHD showed the most autistic symptoms [106].

RRBs seem to appear less often than communication and social deficits in ADHD children [83]. Recently, it has been found that the separation between RRB and social-communicative dimensions is not affected by ADHD in children; these results highlight that they are distinct dimensions, as shown in children with ASD and in the general population [97, 107]. These data indicate that the existence (or non-existence) of ADHD in children does not impinge upon social-communicative deficiencies and RRBs expression. This finding also justifies the DSM-5’s change from a triad to a dyad of diagnostic impairments [35, 38]. However, there appears to be some overlap across RRB traits and hyperactive-impulsive symptoms in children with ADHD [107].

Therefore, it is essential to know to the extent of hyperactivity/overactivity in its most severe form in young children fosters development of autistic traits such as pragmatic language impairment and RRB traits. Future studies conducted on these issues in light of the new criteria in DSM-5 will be of maximum interest.

4.2. Common risk factors susceptibility in ADHD/ASDS

The etiopathogenesis of NDDs appears to be the result of the combined actions of both environmental and genetic risk factors on the developmental process. NDDs display highly complex pathophysiological processes as well as considerable (epi-) genetic heterogeneity. However, NDDs present some phenotypic overlapping in their traits, show a substantial comorbidity and share a number of environmental and genetic risk factors. The current heritability estimates of ASD and ADHD also imply the relevance of common environmental and disorder-specific risk factors for one or both disorders [108].

4.2.1. Genetic risk factors

In recent years, numerous scientific and technical advances have been developed on the human genome. This has allowed an exponential progress in understanding the molecular pathways of genetic expression, which has revealed the pathogenesis of many diseases. In NDD such as ASD and ADHD, these genetic and epigenetic risk factors are very wide, which makes it difficult to give simple answers at the present time. Up to now, genome-wide association studies (GWASs, genome-wide single nucleotide polymorphism (SNP) association studies and

genome-wide copy number variants (CNV) studies), assessments of chromosomal variations, as well as candidate-gene and linkage analyses have revealed an ample spectrum of genes presenting polymorphisms and susceptibility mutations related to ADHD and ASD.

- **Genetic ASD**

We now know that a number of Mendelian syndromes seem to be connected to autism. The most common of these single-gene defects, including CGG repeats within the FMR1 gene as the cause of Fragile X syndrome, mutations in the MECP2 gene in Rett syndrome, tuberous sclerosis, and PTEN mutation, account for but a small minority of cases (for up to 5% of ASDs) [109]. Further, even pooling these syndromes together with cytogenetic abnormalities and other diagnosable medical conditions still only account for <10% of cases. The latest advances made in genetics and technology, mainly the widespread use of molecular techniques by chromosomal Microarray Studies and Next-generation Sequencing, have increased the diagnostic cost-effectiveness of conventional techniques (karyotype, subtelomeric analyses, etc.) from 3–5% to 30–40% in patients with intellectual disability or ASD. Cytogenetic abnormalities at the 15q11-q13 and the 7q22-q37 locus seems most strongly linked to autism. Children presenting congenital abnormalities, dysmorphic traits, mental retardation, or with a family history of developmental disorders are the main population expected to profit from genetic consultation and extensive medical testing. Increased diagnosis of ASD associated with genetic abnormalities has allowed its new specification in DSM-5: “associated with known medical or genetic condition”.

However, for children with “nonsyndromic or idiopathic” ASD, the studies of genetic risk factors have been less conclusive. The rate of recurrence of ADS in siblings of affected children is about 2% [110], which is 16 times higher than in the general population but much more reduced than in single-gene diseases. There is a remarkable concordance in monozygotic twins (60% to 95.2%) as well as in dizygotic twins (0% to 10%), indicating a strong genetic component. Nevertheless, despite the high heritability of ASDs (~90%), the genetic substrate of these syndromes still remains to be fully elucidated [111]. So, only a few loci show recurrent mutations, and these recurrent mutations account for only about 1–2% of patients [112]

Recently, rare, highly penetrant single nucleotide variants (SNV) have been receiving increasing attention as potential sources of “idiopathic autism” [113–117]. Furthermore, most of the uncovered genetic basis for ASDs correspond to rare variants, mainly the X-linked DDX53-PTCHD1 locus, as well as CNVs involving numerous ASD genes such as DLGAP2, SHANK2, and SYNGAP1 [118]. But this only represents a selected sample of examples of the numerous studies in this field, in as much as these CNVs are widely distributed across the genome at more than 100 different loci. The statistical distribution of influences across the genome suggests that hundreds of different human genes can mutate to influence autism risk [117]. Present calculations indicate that CNVs and SNVs occurring in X-linked, recessive or dominant models represent a small proportion of ASD (as many as 15% of cases), and common SNPs constitute almost 50% of the diversity in autism. Several GWASs [119–122] have been performed to decipher the genetic etiology of autism that is attributable to common variants (i.e., SNPs), with only a few variants having shown significant associations and replicated in an

independent population or in endophenotypes. Examining the data from individual SNPs as well as their overall effect that may be deduced from the allele score results, it is acceptable to assume that common variants are implicated in the risk for ASD but individually considered, their effects are moderate

Furthermore, current progress in next-generation sequencing and exome sequencing has allowed the finding of an astounding amount of de novo mutations that increase the risk for ASD. Some of them are copy number variations or rare mutations in synaptic proteins including ProSAPs/Shanks proteins (with a crucial role in the assembly of the postsynaptic density during synaptogenesis, in synaptic plasticity, and in the regulation of dendritic spine morphology) [123], and neuroligins/neurexins (synaptic cell adhesion molecules that play a pivotal role in the assembling of both inhibitory GABAergic and excitatory glutamatergic synapses in the brain) [124]. It has been proposed that genes implicated in "monogenic" variants of syndromic and nonsyndromic ASD coincide on molecular pathways and mechanisms related to synaptic dysfunction (developmental synaptopathies). These genes would regulate synaptic protein degradation and synthesis including neurotransmitter receptors and postsynaptic scaffold structure, and would be involved in synaptic development, plasticity, and signaling [125].

It is not yet clear whether the same group of genes that are involved in the usual genetic risk factors are the same genes that can also cause ASD through rare, highly penetrant mutations. Besides, despite all the research devoted so far to identifying the biochemical pathways involved in ASDs to unify diverse genes, conclusive, well-replicated evidence is not yet available. The mechanisms by which these mutations produce ASD syndromes have only been very partially elucidated [for review see 126, 127]. Hence, genetic factors in most cases still remain unknown, but may potentially include complicated processes such as gene-environment interaction or gene-gene interaction, or even less penetrant rare variants. In this way, one might conclude that the interplay between a variety of genes can produce "idiopathic" autism but that exposure to environmental modifiers as well as "epigenetic factors" may add up to a varying expression of autistic features [128].

- **ADHD and its candidate genes.**

ADHD clinical expression presents a high degree of heterogeneity and not only genetic but also environmental factors are implicated in its etiology. A meta-analysis of 20 pooled twin studies estimated an average heritability of 76%, suggesting that ADHD is one of the disorders with the strongest genetic component in psychiatry [129]. In spite of its high heritability estimates, identifying the genes responsible for ADHD susceptibility has become a complicated and slow task. In recent years, numerous molecular genetic studies (more than 300, including: genome-wide CNV studies as well as genome-wide and candidate-gene association studies) have been devoted to find susceptibility loci for ADHD. The first genetic studies in this field focused on genes related to the dopaminergic system. However, only small effects were found and they could explain just a small fraction of ADHD heritability. The latest studies are trying to identify new genes and pathways underlying ADHD [for review see 130, 131].

The release of linkage studies has provided more than 100 different regions for ADHD including 6q12, 4q13.1, 16p13, and 17p11. Until now, candidate-gene association studies (CGASs) have been able to propose close to 180 candidate genes. The foremost types of pathways involved are the neurotransmission systems: dopaminergic neurotransmission system (mainly DRD4 and dopamine transporter gene DAT1 or SLC6A3), serotonergic candidate genes (HTR2A, DDC, and MAOB), and noradrenergic genes (SLC6A2, ADRA1B). Other neurotransmitter transporters, such as serotonin receptors HTR1B, HTR2A, and HTR2C; adrenergic receptors ADRA2A and ADRA2C; and cholinergic receptor CHRNA4 were also on the list of “hot genes”. In addition, common variants in 16 genes implicated in the control of neurotransmitter release were evaluated [132], as well as a member of the cytokine family of NTFs (CNTF), 10 genes encoding for four neurotrophins (NTF3, NTF4/5, BDNF, and NGF), and their receptors (CNTFR, NGFR, NTRK1, NTRK2, and NTRK3) [133]. Other promising genes: identification of the *LPHN3* gene, a member of the latrophilin subfamily of G-protein-coupled receptors involved in GABA-ergic neurotransmission. Furthermore, the influence of gender factors such as neurosteroids has been of interest, as well as the STS gene.

The results from the five GWASs of ADHD published so far show 85 genes presenting single nucleotide polymorphisms connected with ADHD at a p value <0.0001. Data showed that 45 out of the 85 top-ranked ADHD candidate genes encoded proteins pertaining to a neurodevelopmental pathway implicated in directed axonal outgrowth. SNPs with nominal associations have been identified for several candidate genes such as CHRNA4, SYT1, ADRB2, DRD2, HTR2A, SLC9A9, SLC6A2, TPH2, and BDNF. SLC9A9 seemed to be the most promising candidate out of these findings [130]. Of the identified genes, some (i.e., BMP2, NRXN1, SERPIN1, NAP5, NOS1, ZNF423, SERPIN1, ERK1, NEDD4L, and CTNNA2) are placed within copy number variations and are therefore duplicated/deleted in ADHD patients. Several network proteins are also directly modulated by stimulants, the most commonly used psychopharmacological treatment for ADHD [134].

- **Shared genetic susceptibility ADHD/ASD**

Numerous family studies have revealed that relatives of patients with either ASD or ADHD frequently display features of the other syndrome [91, 135, 136]. Twin studies have highlighted that quantitative variation in the characteristic behaviors from these two disorders may share genetic risk factors. According to twin studies, which used questionnaire-based data on ADHD and ASD symptoms, about 50–70% of the co-variance of ASD and ADHD symptoms may be explained by shared additive genetic factors [93, 137–139]. Presence of ADHD in the parents can predict ASD in the offspring, but not conversely. Therefore, risk factors at the root of ASD may overlay to a greater extent with ADHD risk factors than vice versa [140].

Even though genetic data support the notion of a shared genetic background for both types of syndromes, not many GWA, candidate gene or linkage studies, have specifically investigated ASD/ADHD co-occurrence. Nonetheless, they are providing some promising, loci SNPs and pleiotropic genes [for review see 1, 83, 84].

- *Linkage and candidate gene association studies:* As potential-specific candidate genes for ADHD (functional), variants predominantly in dopaminergic and serotonergic genes have been

described [138, 141]. Several variants in candidate genes of ADHD have also been examined for their potential association with ASD: variants in DAT1, DRD3, DRD4, catechol-O-methyltransferase (COMT), and monoamine oxidase A (MAOA) [142]. Only DRD3 and MAOA variants were nominally associated with ASD symptoms [84].

- *Genome-wide association studies (GWAS)*: Interestingly, It has been recently discovered that both rare variations and common polymorphisms in one single gene or genetic locus bear susceptibility for conditions up to now thought to be etiologically and clinically distinct. Results of CNV studies supported evidence of a shared heritability in ADHD and ASD. In ADHD cohorts, CNV enrichment was observed at loci linked with autism. Common genetic risk regions were reported for 1p36, 1q21.1, 15q11.2–q13.1, 15q13.3, 16p11.2, and 22q11, respectively, and the genes CNTN4, SUMF1 (sulfatase modifying factor 1), NLGN1, AUTS2 (autism susceptibility candidate 2), UBE3A, and DPP6 [for review in detail see 81, 84]. ASD/autistic-like traits (ALTs) have been linked to polymorphisms in a number of genes implicated in synaptic physiology in the autism candidate regions (RELN, CNTNAP2, SHANK3, and CDH9/10); however, these findings have not been confirmed in all studies [143].

Thus, the possibility exists that the pathological pathways underlying ASD/ADHD share some genetical background; for example, the serotonin transporter, 5-HTT, has been associated with both conditions [144,145] and SNP (rs4307059), between the genes Cadherin 9 and 10 (*CDH9* and *CDH10*), has been associated with ASD and social interaction impairment [143].

The results of exome sequencing studies support models of significant polygenicity for autism; current studies may allow the identification of these genes and elucidation of the repercussions of their products on brain physiology and development [for review see 2, 109, 112, 120, 146]. In light of research of the etiology of these traits, we may come to understand the high heritability and co-heritability of both disorders. On the other hand, the results cannot rule out that the same genotype may be expressed as a distinct ASD or ADHD phenotype [142].

4.2.2. Non-genetic biological risk factors

Although genetic contributions to autism and ADHD etiology are well accepted, the rising prevalence and inconsistent findings from genetic studies suggest a role for interactions between susceptibility genes and relevance of environmental factors for both disorders. Compared with the magnitude of genetic studies in ASD and ADHD, non-genetic biological risk factors besides the well-known male preponderance in both disorders have rarely been studied. The relationship between sex/gender differences has also attracted a variety of research [147,148].

Among the pregnancy-related risk factors that have been associated simultaneously with ASD and combined ADHD diagnosis or symptoms, are toxic exposures and teratogens (as in the use of valproic acid), maternal diabetes, pre-pregnancy obesity, pre-eclampsia, and viral or bacterial infections; these, however, account for few cases. Similarly, studies on maternal autoimmune disorders during pregnancy have reported different associated disorders (psoriasis with ASD; thyroid antibodies with ADHD). Prenatal inflammation and prematurity

must be mentioned, associated simultaneously with both ADHD and autism. [81]. A growing body of literature suggests that certain modifiable risk factors such as maternal metabolic syndrome and intake of certain vitamins such as vitamin D and folic acid either in utero or early life, may be associated with increased risk of autism [24, 149].

Previous research has not been able to prove that administrations of the measles-mumps-rubella vaccine were connected with the **autism upsurge** [23], but it has been suggested that acetaminophen may mediate oxidative stress and neurotoxicity in autism [150, 151], and exposure during pregnancy enhances the probability of appearance of ADHD-like behaviors [152]. These are data from an ecological analysis, not considered optimal as evidence of causality. Nonetheless, there is accumulating clinical and experimental evidence connecting acetaminophen metabolism to biochemical routes known to be relevant for autism and related developmental disorders. Taking into account both ecological and mechanistic evidence, the role of acetaminophen in autism should be formally studied [153].

4.3. Common neurobiological substrates

The human brain is an organ of high biological complexity consisting of many different regions, neural pathways and billions of functionally distinct cells. Moreover, it presents a very complex, highly regulated development that extends for a prolonged period of time and involves deep morphofunctional changes. These processes depend on appropriate gene expression producing unimpaired mRNAs and proteins. Mutations altering gene products or function may favor or lead to psychiatric or neurological disorders [154].

Current knowledge indicates a crucial role for the impairment of strictly regulated and well-determined neurodevelopmental processes in NDDs, principally synapse formation and remodeling and neuronal proliferation and migration, aside from configuration of the neural network, causing impaired connectivity and neurophysiology. Furthermore, the epigenetic mechanisms combined with genetic change may alter many of those developmental events and pathways, thus affecting the vulnerability to, and recovery capacity from, NDDs. As a consequence, disease entities such as ID, ASD, or ADHD that are currently categorically defined, are beginning to be regarded as part of a continuum of neurodevelopmental disorders caused by a large variety of cellular and molecular dysfunctions. As it is, the different types of NDDs present a wide phenotypic variability that could be the result of the combination or interaction of subjacent loss and/or gain of function characteristics [155].

4.3.1. Selective brain imaging findings

As we have already mentioned, the origin of ADHD and ASD is multifactorial, and both the etiology and pathophysiology are as yet incompletely understood. The study of neuropsychological profiles across patients with ASD and ADHD has revealed similarities that, in turn, provided evidence for shared neurobiological substrates. ADHD and autism have been associated with prominent executive dysfunction that can derive from impairment within fronto-parietal and fronto-striatal pathways. The prefrontal cortical circuit is in charge of "top-down" regulation of motivation, inhibition/cognitive control, emotion, and attention via

connections with posterior cortical and subcortical nuclei. Inferior and dorsolateral prefrontal cortex (PFC) modulate cognitive/inhibitory control and attention, while ventromedial and orbital nuclei regulate affect and motivation. PFC pathways are highly sensitive to neurochemical conditions, and even modest variations in their neurotransmitter environment (e.g., pharmaceuticals) may cause big effects on their functioning [82, 83].

Neuroimaging work with children with neurodevelopmental syndromes has revealed brain functional and structural impairments in specific pathways regarding this organization [156]. The majority of MRI works investigate just one of the conditions at a time. Several meta-analyses [157–159] have reported decreased brain volume for ADHD patients in most of the studies examined. The main regions affected by volume reductions in ADHD patients were the caudate nucleus, putamen, globus pallidus, and lentiform gyrus. A decrease in total brain volume and grey matter has also been reported in ADHD subjects when compared with standard development control individuals.

It should be pointed out that the development of brain volume alterations differs between ASD and ADHD. In ASD individuals, the brain seems to undergo an accelerated growth stage during the first four years of life, until achieving a plateau level similar to standard development around puberty. However, this is succeeded by a decrease in brain volume towards adulthood in comparison with standard development controls. It is also noteworthy that younger children with autism (2–3 years old) show an increase in white matter (WM) greater than an increase in grey matter (GM) (18% more WM in the cortex and 38% more WM in the cerebellum). This increment in WM found in young children is inverted in 12–16-year-olds with autism whose WM volume is decreased when compared with healthy children [160]. Histopathological analyses have shown that children with autism present an excessive number of neurons in the prefrontal cortex, indicating impairment in prenatal development that can be accompanied by abnormal laminar development and dysmorphic cell types. Qualitative neuropathological developmental changes in 92% of autistic individuals reveal multiregional impairment of maturation, neuronal migration, and neurogenesis in autism, which could be an additional source of heterogeneity in their clinical phenotype [161]. Recent data support a likely failure in the regulation of layer-specific neuronal differentiation and layer formation during the antenatal brain developmental period [162]. Although many cell types and brain areas can be damaged, the main effect of ASD related mutations seems to be on the medium spiny neurons of the striatum and cortical pyramidal neurons and interneurons, suggesting the involvement of corticostriatal and cortical pathways [127].

It seems likely that ASD represents a disorder with more general abnormalities and atypical connectivity compared to ADHD. Functional and structural brain connectivity studies in individuals with these conditions have provided initial evidence regarding apparent overlaps in the neuroanatomy of the syndromes. Nonetheless, data have not been consistent across studies, which could explain both the convergent and divergent clinical and behavioral manifestations.

A structural MRI study [163] in 15 children and adolescents with ASD, 15 age-matched ADHD patients and 15 healthy peers described several brain volume variations across both patient groups relative to the control, such as increased GM volume in the left inferior parietal cortex

and a decrease in GM in the left medial temporal lobe. Furthermore, they also found an increment in GM volume in the right supramarginal gyrus that was specific for autism. By contrast, Ray et al. [164] suggested that ASD and ADHD display differential large-scale connectivity patterns in intermediate childhood. The ADHD group showed reduced functional connectivity and generalized fractional anisotropy (GFA) inside the rich-club networks, but elevated correlation coefficient values and number of axonal fibers outside the rich-club. Other studies have also identified implication of sub-cortical arousal systems and frontoparietal attention networks in ADHD pathology, as well as prefrontal cortex malfunction in children with HFA [165].

In a comorbidity study, increasing ASD scores in ADHD were associated with greater GM volume compared with the typically developing population [166]. Recent work by Geurts et al. [167] has found that volume variations in some specific brain areas are often associated with the severity of ASD and ADHD symptoms. Volumetric changes in the left inferior frontal gyrus GM were associated with symptom severity in both conditions. Variations in the left posterior cingulate GM volume appeared to be ASD specific, whereas the bilateral thalamus, left hippocampus/amygdala complex, right temporal frontal cortex, and right parietal lobe seemed to be specifically correlated with ADHD symptom severity. This work suggests that ASD and ADHD constitute a continuum expanding into the broad population. Nonetheless, the conclusions were marred by the fact that the directions of the brain-behavior relationships lacked consistency across regions when compared to previous clinical reports.

4.3.2. Neurotransmitter systems

- **Catecholaminergic pathways:** The catecholaminergic pathways have been a usual focus for ADHD neurobiological research on ADHD since they represented the principal target for drug treatments. The neurotrophic factors (NTFs) participate in synapses formation, neuronal survival, and neurodevelopment, whereas the dopaminergic and serotonergic systems are implicated in neurotransmission, cortical organization, and brain maturation. The “monoamine deficit-hypothesis” of ADHD postulates an imbalance in the interaction of the neurotransmitters dopamine, noradrenaline, and serotonin. The neurotrophic factors as well as the neurotransmitter systems are thought to be good candidates for ASD and frequent allelic variants in the dopamine decarboxylase (DDC) gene may be connected with susceptibility to autism [142].

Notwithstanding, more basic and distal neuronal mechanisms connected with cell functionality and morphology could also play a role, possibly providing an explanation for the coexistence of both specific and diffuse impairment in brain activation patterns and structure [for review in detail see 168]. For both disorders (ADHD/ASD), the association with the serotonergic system is a focus of current research [169].

- **The imbalance of excitatory/inhibitory neurotransmitters:** Excitotoxicity, oxidative stress, and impaired mitochondrial function are mechanisms that potentially serve as convergence points for these genetic, environmental and immunological risk factors in both disorders. A balance between excitatory glutamate and inhibitory GABA neurotransmitter is essential

and critical for proper development and functioning of the brain. GABAergic (gamma aminobutyric acid) and glutamatergic interneurons maintain excitability, integrity, and synaptic plasticity. Glutamate is the principal excitatory neurotransmitter in the central nervous system. Glutamate hypersecretion as well as hyperactivity of its NMDA and AMPA receptors are known to produce excitotoxicity via the activation of enzymes that injure cellular components and alter membrane properties and electrochemical gradients [170]. Many synaptic protein genes are linked to the pathogenesis of ASDs, making them prototypical synaptopathologies. For excitatory glutamatergic and inhibitory GABAergic synapses, neuroligins (trigger postsynaptic differentiation), and neuroligins (trigger presynaptic differentiation) play a pivotal role in synaptic function, especially at GABAergic synapses. Several works have implicated relative loss of inhibitory GABA with corresponding glutamate-mediated hyper-excitation in the development of ASD and ADHD, which might resemble a common pathological mechanism for these developmental disorders [171].

- **Neurosteroids:** Increasing evidence shows gender differences in the clinical manifestations and pathology of a number neurodevelopmental syndromes, including ADHD and ASD, likely via the effects of sex hormones during critical stages of brain development. Moreover, neuroactive steroids are known to be involved in modulation of neuronal excitability, synaptogenesis, spinogenesis, as well as neuroprotection through binding GABA A-type receptors [172]. Symptoms of cognitive and attention-related deficits have been observed in boys with X-linked ichthyosis caused by a mutation at the STS gene [173]. The STS gene can be found on the distal part of the short arm of the X chromosome (Xp22.3-pter), and a higher prevalence of ADHD in boys than in girls is characteristic of the disorder. This gene is responsible for conversion of the sulfated form of dehydroepiandrosterone (DHEA), known as DHEA-S, to DHEA. Neurosteroids are important neuroactive substrates with demonstrated involvement in ADHD, with significant inverse correlations between levels of both DHEA and pregnenolone and clinical symptomatology [174]. It is interesting to note that the STS gene escapes X-chromosome inactivation, thus a possible differential influence on ADHD in girls should also be considered in future studies.

5. Impact of comorbid ADHD and ASD: A continuum?

Research on co-occurring ADHD and ASD has been limited by diagnostic restraints, since according to DSM-IV, many works have excluded subjects with more than one developmental or psychiatric disorder [175]. The study conducted by Sinzig et al. [176], reveals a large phenotypic overlay between ADHD and ASD. The two identified subtypes, hyperactive-communication impaired and inattentive-stereotyped, follow the DSM classification and could be the manifestation of two distinct neurochemical circuits—dopaminergic and serotonergic—involved in the disorders. In view of this, the division of ASD into two-dimensional scales of social-communication and RRB dimensions, and of ADHD into inattentive and hyperactive-impulsive symptoms has high significance for the classification of developmental conditions.

The debate continues in the literature regarding the clinical implications of these findings; some authors believe that co-occurring symptoms indicate the existence of two distinct

syndromes with a common etiology [177], whereas other researches argue that these conditions are better explained as part of one ample spectrum, extending from moderate (ADHD) to more serious (ASD) disability [82]. There is accumulating evidence indicating that ASD and ADHD are at both ends of a continuum, instead of being different entities [139, 178, 179]. It is especially important to establish the diagnosis of co-occurrence of both entities, since symptoms such as limited attentional bias toward people in early development is expected to have deleterious consequences on the appearance of social interaction patterns and the maturation of brain social networks. Further research into the underlying substrates of decreased social attention and its role in the psychopathology of ASD in the first year becomes necessary [57].

6. Therapeutic interventions for co-occurring ADHD and ASD

Recent findings associate co-occurrence of ASD and ADHD in children with poorer quality of life and decreased adaptive functioning in comparison with data from children suffering from ASD only. Adolescents diagnosed with both ASD and ADHD appear to need psychiatric medication more frequently (58%) than young people with ASD (34%) or ADHD (49%) alone. Moreover, co-occurrence of ASD and ADHD seems to make individuals less sensitive to current therapies for either condition than patients with only one of the syndromes [180, 181]. Only a few specific studies on a targeted treatment for children, adolescents, and adults with comorbid ADHD and ASD have been performed to date. The improvement of current treatments will require a better understanding of the mechanisms underlying co-occurrence of ASD and ADHD (for review see 1, 81, 82, 175, 182).

6.1. Psychoeducational/behaviorallybased interventions

ASD/ADHD should allow for more targeted interventions. Parent-mediated interventions can be markedly effective during early infancy, since parental behavior influences both social-communicative learning and the development of executive functions [183]. The identification of common protective factors could be of pivotal importance, since interventions targeting those factors would apply to a wide spectrum of conditions. Furthermore, determining which early risk factors are responsible for cascade effects and which are a mere reflection of the pathological process could be important for identifying the main intervention targets [85]. In preschool children with ASD, the treatment of choice is behaviorally-based early intervention [184, 185]. Likewise, in older schoolage children with ASD, autism-specific social skills training leads to improved social responsiveness [186–188]. Still, despite this treatment intensity, not all children with ASD improve with therapy [189].

By contrast, in a Cochrane Database review of randomized trials studying social skills training for children with ADHD as a standalone therapy or as a complement to pharmacological treatment, the data suggest that there is not enough evidence either to support or refute social skills training for youths with ADHD [190]. In this sense, another meta-analysis [191] compares effect-sizes of psychosocial treatments and methylphenidate and their combination on ADHD, academic functioning, concurrent conduct and oppositional symptoms, and social behaviors.

Both psychosocial treatments and methylphenidate are effective in decreasing ADHD symptoms. However, psychosocial treatment renders more modest results than the other two treatments, and adds no further benefit to methylphenidate for the improvement of teacher-rated oppositional defiant disorder symptoms and ADHD.

In a recent study to evaluate the influence of psychiatric comorbidity on social skill treatment effects in children with ASDs, it was found that while children with ASD and comorbid symptoms of anxiety improved by social skills training, children with ASD and comorbid ADHD did not [180].

6.2. Pharmacological interventions

The clinical impairments associated with ASD are often difficult to alleviate, and are increasingly managed using pharmacologic interventions. While core symptoms of communication deficits and circumscribed interests are difficult to address with medication, other clinical impairments are often targets of treatment, including comorbid anxiety, difficulty with sustained attention, aggressive behaviors, sleep disturbances, and stereotypic movements [for review see 175, 192, 193].

The only medical treatments passed by the United States of America Food and Drug Administration (US FDA) for ASD are the antipsychotic drugs risperidone (Risperdal) and aripiprazole (Abilify). However, these pharmaceuticals only address one symptom connected with ASD, irritability, but none of the core ASD symptoms, and treatments for ASD remain limited. Despite the lack of extensive evidence and unclear effectiveness, examination of prescribing patterns for youth with ASD reveals that pharmacotherapy is very common, and many other medications may be prescribed off-label. The strongest evidence for a positive effect comes from noradrenergic reuptake inhibitors, alpha-adrenergic agonists, antipsychotics, and psychostimulants [193]. Further work is necessary to determine subgroups of children with ASD in which these treatments would be most effective and confirm their efficacy in double-blind, placebo-controlled large-scale multicenter studies.

6.2.1. Antipsychotic medications

The effectiveness of risperidone and aripiprazole for irritability associated with autism is supported by several articles reviewing the literature. All conclude that the data supporting effectiveness is strong, while cautioning that behavioral intervention should be tried first, and that side effects including metabolic abnormalities, weight gain, and potential for extrapyramidal side effects warrant caution in their use [192].

6.2.2. Antiepileptic drugs (AEDs)

The impairments in gains of GABAergic transmission could also justify the very high prevalence of epilepsy in autistic patients (about 25%) [194] with respect to the average prevalence of 1% in the general population [195]. Moreover, up to 20–25% of subjects with PDD without epileptic paroxysmal clinical manifestations may present EEG abnormalities, mainly during night polygraphic recordings. A recent large-scale study revealed that ADHD in children is

often accompanied by epilepsy; about half (48.3%) of the children with ADHD had abnormal EEG findings and 22.1% of them had epileptiform discharges [196]. Regression in PPDs associated with seizures and epileptiform electroencephalogram correlates have been reported. [197]. Cases of complete recovery or significant improvement following the use of AEDs such as valproate, ethosuximide, clobazam, oxcarbazepine, sulthiame, levetiracetam, topiramate, or lamotrigine in ASD have been reported. It is speculated that the suppression of subclinical epileptiform activity by the early use of AEDs can reverse the changes in behavior, cognition, and language in these patients and, in a similar way, could improve the semiotic nucleus of ASD. Overall, there are few studies and limited evidence for the use of antiepileptic mood stabilizers in improving symptoms of ADHD in children with PDDs and the positive studies in ASD are all uncontrolled. Despite some positive carbamazepine studies in typically developing children, clinical use of these agents for ADHD symptoms in children with PDDs must be considered a personal experiment and should be guided by clinical data [193]. An electroencephalogram (EEG) is recommended in young children with ASD or ADHD, and can help confirm whether a child is having seizures. But even if they are not having seizures, these children may have abnormal EEGs, and additional antiepileptic drug treatment is advisable.

6.2.3. Psychostimulant medications

- **Methylphenidate:** Psychostimulant medication, most commonly the catecholamine agonist methylphenidate (Ritalin®) and OROS-methylphenidate (Concerta®), is the safest and most effective treatment for people with ADHD. The prevalence of stimulant treatment in youth with ASD is 16% [198]. Methylphenidate's mechanism of action implicates the inhibition of catecholamine reuptakes; it acts by arresting the norepinephrine and dopamine transport, leading to elevated concentrations of norepinephrine and dopamine in the synaptic cleft. Methylphenidate is also a 5HT1A receptor agonist. The fMRI analysis showed that methylphenidate significantly enhanced activation in the bilateral inferior frontal cortex/insula during inhibition and time discrimination but had no effect on working memory networks [199]. These areas of the brain are fundamental to cognitive control and the most replicated neurocognitive dysfunctions in ADHD occur here.

Methylphenidate is clearly effective in treating children with ASD and hyperactive symptoms or comorbid ADHD, but a lower daily dose is generally required [200]. However, not all children with ASD benefit from methylphenidate treatment and those who respond present more side effects than children with ADHD. A recent review of randomized and non-randomized trials concluded that, after careful symptom assessment, treatment of comorbid ADHD symptoms with stimulant medication is indicated for youth with ASD [201].

All in all, the stimulants tend to produce highly variable responses in children with PDDs and ADHD symptoms. Such responses range from substantial improvement with minor side effects to more problematic behavior and physical and/or behavioral side effects. Given what we know, stimulants would still be a reasonable first therapeutic choice for previously-untreated children with PDDs and uncomplicated ADHD, even though they do not work as well, on average, as they do in typically-developing children. Any side effects should be reversible on discontinuing the drug. Clinicians should be candid with parents about the lower

likelihood of a positive clinical response and elevated risk of adverse events. Treatment should proceed with low initial doses, small dose increments, and a data-based approach. Both clinicians and parents should be prepared to stop the trial if there is clear evidence of behavioral deterioration and/or unacceptable adverse events [193].

- **Lisdexamfetamine dimesylate (LDX)** is a once-a-day medication passed by the US FDA as a possible treatment for ADHD management in children (6–12 years of age) as well as in adults [202]. It is generally employed in children and adolescents with an inadequate response to methylphenidate (MPH) treatment, but to date, there are no studies of its use in ASD.

6.2.4. Nonstimulant Medications

- **Noradrenergic reuptake inhibitor: Atomoxetine (Strattera®).** There is some evidence for effectiveness of non-stimulant ADHD medications in youth with ASD. They also alleviate ADHD symptoms in both disorders; with one randomized controlled trial [203] each for atomoxetine, which showed superiority over placebo. Generally speaking, methylphenidate and atomoxetine present similar efficacy and the same acceptability in treating children and youths with ADHD. Nonetheless, OROS-methylphenidate seems more effective than atomoxetine and can be considered as first line treatment of ADHD in children and adolescents [204].
- **Alpha2 Adrenergic Agonists:** Clonidine and guanfacine act on α 2-adrenergic presynaptic receptors to inhibit noradrenergic release and synaptic transmission. Guanfacine has a longer action than clonidine. Guanfacine is an alpha-2 adrenergic agonist traditionally employed for hypertension treatment that has been recently approved to treat ADHD as an extended release formulation. Ituniv® (Shire; Dublin, Ireland) can be used both alone and together with stimulants for the treatment of children with ADHD [205]. Several studies report positive results for guanfacine treatment in children with co-occurring ADHD and ASD symptoms. Reduction in hyperactivity and inattention among cognitively higher-functioning (i.e., not cognitively-impaired) children with ASD was found in a retrospective analysis of 80 clinical patients [206]. Similarly, in an open trial studying children for whom methylphenidate was previously unsuccessful, guanfacine had positive effects on parent- and teacher-rated hyperactivity [207].
- **Selective serotonin reuptake inhibitors (SSRIs):** Although fluoxetine (Prozac) seemed to be beneficial for some autism symptoms, the increase in hyperactivity may be a limiting factor. A Cochrane Review concluded that there was no systematic evidence to support the use of SSRIs to treat ASD [208].
- **Cholinesterase Inhibitors: Donepezil, Galantamine, and Rivastigmine Tartrate.** To date, there is no compelling argument for advocating cholinesterase inhibitors for treating either the secondary symptoms or the core features of autism. Rigorous exploratory studies are needed. Galantamine can be of possible benefit for interfering behaviors in children with PDDs, although there was no indication of benefit for ADHD symptoms [209].

- **NMDA receptor Antagonists:**

- **Amantadine**, which impacts the N-methyl-D-aspartate (NMDA) receptor, may act by limiting excitotoxicity of the glutamatergic neurotransmitter system. This receptor class is thought to be essential for modulating synaptic plasticity and represents a new class of pharmacologic targets with the potential to impact neurophysiologic and cognitive functioning. One RCT of amantadine treatment in youth with ASD found improved control of irritability and hyperactivity [210], and another reported beneficial effects for ADHD [211]. Although amantadine is not commonly used, it may be considered when other treatments do not provide adequate symptom control, particularly for distractibility and hyperactivity [192].
- **Memantine** is an NMDA antagonist that is thought to preserve neuronal function. It selectively blocks the excitotoxic effects associated with abnormal glutamate transmission by modulating calcium channels. Treatment with memantine is clearly experimental at this time.
- **Antioxidants:** Oxidative stress and antioxidants can participate in pathobiochemical mechanisms of autism. Chemicals standardly employed for mitochondrial disorder treatment have been shown to alleviate both core and associated ASD symptoms [for review see 212, 213]. Two DBPC studies employing a multivitamin complex containing antioxidants, co-enzyme Q10, vitamin E, and B vitamins showed several improvements in ASD symptoms when compared to placebo administration [214, 215]. Several other antioxidants, including vitamin C [216], methylcobalamin and folic acid [217–219], N-acetyl-L-cysteine [220–222], ubiquinol [223], and L-carnosine [224], have also caused significant progress in ASD behaviors and may work to enhance mitochondrial function without causing adverse effects; therefore, they could be recommended in younger children.
- **Bioactive lipid mediator:** Many animal and clinical studies have shown the relevance of long-chain polyunsaturated fatty acids (LCPUFA) in neurodegeneration and neural development [225]. Increasing evidence indicates that altered fatty acid metabolic pathways as a result of insufficient dietary supplementation or genetic defects, may affect proper function of the nervous system and contribute to ASDs [226]. Many reports have connected ROS-mediated damage with cell membrane loss of integrity and the consequent elevation of intracellular Ca^{2+} , which, in turn, stimulate a number of Ca^{2+} dependent enzymes such as phospholipases and PKC, damaging membranes directly and initiating the production of lipid mediators, including arachidonic acid and platelet-activating factor (PAF).
- **Omega-3 fatty acids** may improve ADHD symptoms, but large randomized-controlled studies need to be done [227]. A recent Cochrane Review did not find any evidence of effects of Omega-3 fatty acids in ASD [228].
- **Citicoline (cytidine diphosphate-choline):** Although the exact mechanisms by which citicoline produces its neuroprotective effects are unknown, the suggested mechanisms that may explain the neuroprotective actions of citicoline include stimulation of phosphatidylcholine synthesis, prevention of fatty acid release, restoration of Na^+/K^+ -ATPase activity, increase of glutathione synthesis and glutathione reductase activity, ant glutamatergic

effects, and preservation of cardiolipin and sphingomyelin levels. Additionally, studies indicate that citicoline supplements elevate dopamine receptor concentrations, and cholinergic neurotransmission, and may possibly be useful in the treatment of ADHD [229, 230].

The relationships between betaine, choline, and energy metabolism in the human species suggest new roles for those molecules. These novel functions may surpass the role of nutrients in gene methylation (epigenetic control.) Research simulating methyl-deficient diets has shown impairment in liver protein synthesis and energy metabolism, as well as muscle disorders and fatty liver. Altered levels of total homocysteine (tHcy) in plasma are a good example of how metabolism can be affected by methyl group deficiency or nutrient supplementations. Both elevation of tHcy and hypomethylation can be reduced if either betaine or choline is available [231].

Citicoline given to youth with ASD led to increased control of hyperactivity, reduced attention deficit and improved communication skills in some children [173]. The use of citicoline in young children (prior to three years), followed by methylphenidate after three years, may be an alternative treatment for community pre-schoolers with ASD.

• **Other Agents:**

- **Oxytocin** has also received attention as a potential treatment for ASD. A recent editorial cautioned against premature clinical use as a treatment modality until more research is done to elucidate long-term implications and potential side effects or problems [232].
- **Opiate Blockers:** Several studies of **naltrexone** were conducted in children with autism, usually with the hope of reducing its core features. No consistent effects were found for autism symptoms. However, what is intriguing is that in all of these studies, reductions in hyperactivity were observed, an often unanticipated finding [211].
- **Sleep medication:** Consistent positive effects for melatonin and clonidine were found in autism. However, given the limited data available, a recent review suggested that the most prudent initial course is to formally evaluate patients for sleep disorders, without clear support for any one particular sleep medication [233].

7. Conclusion: Implications for future research

In light of the new DSM-5 criteria, which allow a dual diagnosis of ASD and ADHD behaviors, further investigation into clinical overlap of these two conditions will possibly enhance our understanding of the etiology/genetics factors and common metabolic pathways of these disorders, and of the appropriate sequence of therapeutic interventions and pharmacological treatment for their co-occurrence, particularly in early preschoolers. It remains to be seen whether early intervention could change the course of “ASD in statu nascendi”, interpreted as a continuum with other NDDs such as ADHD or SCD of less than severe character.

8. Nomenclature/abbreviations

AD: Autistic disorder

ADHD: Attention-deficit/hyperactivity disorder

AS: Asperger syndrome

ASD: Autism spectrum disorder

DSM: Diagnostic and statistical manual

HFA: High-functioning autism

GM: Grey matter

NDD: Neurodevelopmental disorders

PFC: Prefrontal cortical circuit

PDD: Pervasive developmental disorder

PDD-NOS: Pervasive developmental disorder-not otherwise specified

RRBs: Restricted repetitive behaviors, interests, and activities

SCD: Social (pragmatic) communication disorder

SNV: Single nucleotide variants

WM: White matter

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